PhRMA

April 28, 1998

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BY MESSENGER

Ms. Robin Kawazoe
Director, Science Policy & Planning Office
National Institutes of Health
Building 1, Room 218
Bethesda, MD 20892

RE: NIH Data Bank—Clinical Trials For Serious Diseases
PhRMA Recommended Approach To Implementing FDAMA §113

Dear Ms. Kawazoe:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry input on Section 113 of the FDA Modernization Act of 1997 (FDAMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies; PhRMA members invest over $20 billion annually in discovering and developing new medicines.

As you know, FDAMA §113 requires the Secretary of Health and Human Services to establish a program within the National Institutes of Health (NIH) to create a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions. In establishing the data bank, it will be important for NIH to balance a range of interests recognized by Congress, including enhancing patient access to clinical trials and protecting the confidentiality of proprietary information. The attached comments, which were prepared by the PhRMA Clinical Trial Data Bank Work Group, address these and other key implementation issues. The Work Group is available at your convenience to discuss this recommended approach and answer any questions.

Sincerely yours,

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cc: Theresa Toigo, Associate Commissioner, FDA
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PhRMA Recommended Approach
FDAMA § 113 – Data Bank

Pharmaceutical Research and Manufacturers of America
RECOMMENDED APPROACH TO IMPLEMENTING
FDA MODERNIZATION ACT § 113
NIH DATA BANK--CLINICAL TRIALS FOR SERIOUS DISEASES

Introduction

Section 113 of the Food and Drug Administration Modernization Act of 1997 adds a new subsection (j) to section 402 of the Public Health Service Act (PHSA) (42 U.S.C. § 282) requiring the Secretary of Health and Human Services to establish a coordinated program within the National Institutes of Health (NIH) to create, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

As set forth in the statute (see numbered comments below), the data bank must include a registry of clinical trials with information on study purpose, eligibility criteria, trial sites, and a contact person. Once the program is established, a study sponsor must forward such information to the data bank within 21 days "after the approval of the protocol" to test the effectiveness of the drug. With the consent of the sponsor, the data bank may also include information pertaining to the results of the clinical trials, including information concerning potential toxicities or adverse effects associated with the use or administration of the treatments. Information relating to a trial will be excluded from the data bank if the sponsor provides a detailed certification that disclosure of information

would substantially interfere with the timely enrollment of subjects, unless the Secretary of HHS responds with a detailed written determination to the contrary.

As Congress recognized in enacting Section 113 of the FDA Modernization Act, it is important to strive to enhance patient access to clinical trials and broaden the pool of research participants. Programs that accomplish these goals, such as registries and databases, benefit both the public health and drug sponsors by speeding patient access to investigational therapies and accelerating the scientific evaluation of the safety and effectiveness of the new therapies. At the same time, such programs must be designed appropriately to balance patient access to fundamental trial information with a drug sponsor's need to maintain the confidentiality of proprietary information, as Congress also recognized in enacting Section 113. The new statutory provision captures this important balance by ensuring that the data bank will include the basic information on clinical trials for serious or life-threatening diseases that is necessary for potential participants in clinical trials to pursue enrollment, without mandating that additional detailed and proprietary information be provided by drug sponsors.

In order to ensure that Section 113 is implemented in an appropriate manner consistent with congressional intent and other NIH and FDA programs, several key issues will need to be addressed, including:

(1) identifying serious or life-threatening diseases and conditions;

(2) identifying which types of clinical trials are appropriate for inclusion in the data bank (e.g., efficacy trials as opposed to safety trials on healthy subjects);

(3) avoiding duplication with other clinical trial registries and databases;

(4) clarifying when sponsors must submit information to the data bank;

(5) ensuring the integrity and reliability of information in the data bank;

(6) clarifying that information submitted to the data bank does not constitute advertising for study subjects;

(7) confirming the applicability of the data bank to all clinical trial sponsors; and

(8) following the statutory directive that including clinical trial results is optional and remains a matter of sponsor discretion.

1. Serious or Life-Threatening Diseases and Conditions

The data bank created by Section 113 applies only to clinical trials of experimental treatments for "serious or life-threatening diseases and conditions." PHSA § 402(j)(3); 42 U.S.C. § 282(j)(3). NIH should identify serious or life-threatening diseases and conditions in a manner that is consistent with other FDA programs that apply to serious or life-threatening diseases and conditions, including (1) the fast track provisions of Section 112 of the FDA Modernization Act for products that demonstrate the potential to address unmet medical needs for a serious or life-threatening condition (Federal Food, Drug and Cosmetic Act (FFDCA) § 506; 21 U.S.C. § 356); (2) FDA's regulatory accelerated approval program for drugs for serious or life-threatening illnesses (21 C.F.R. Part 314 Subpart H); (3) Treatment INDs for serious or immediately life-threatening diseases (21 C.F.R. § 312.34); and (4) Subpart E procedures for drugs intended to treat a life-threatening or severely debilitating disease (21 C.F.R. Part 312 Subpart E). The sponsor of a drug that has received a fast track or accelerated approval designation from FDA, or is subject to a Treatment IND or a Subpart E program should be required to contribute information to the clinical trials data bank pursuant to Section 113.

2. Covered Clinical Trials

Under Section 113, only information concerning trials that test efficacy must be sent to the data bank. PHSA § 402(j)(3)(A); 42 U.S.C. § 282(j)(3)(A) (information must be sent to registry "when a trial to test effectiveness begins"). Accordingly, Phase I trials should be excluded from the data bank, because Phase I trials are usually conducted in healthy volunteers and are not designed to establish efficacy of new agents. Phase II trials that do not include efficacy endpoints should also not be sent to the data bank. Similarly, Phase IV (post-approval) studies should not be reportable, because patient awareness of and access to the medicine has necessarily already been achieved. The focus for the data bank should be on efficacy trials where the sponsor has some idea of the dose and the potential effectiveness of the study compound, and patients can most benefit from information regarding drug development. Requiring the inclusion of Phase I, certain Phase II, and Phase IV trials would only burden study sponsors without furthering Congress' intent of enhancing patient access to clinical trials and broadening the pool of research participants.

In implementing Section 113, NIH should also provide that (1) only clinical trials with U.S. trial sites should be included in the data bank; and (2) expanded access protocols developed pursuant to Section 402 of the FDA Modernization Act (FFDCA §561) need not be reported for inclusion in the clinical trial data bank.

With regard to the expanded access provision of FDAMA, it makes no sense to place information regarding single patient protocols in the data bank (see FFDCA §561(b)). As for expanded access sponsor/physician treatment INDs (see FFDCA §561(c)), section 402 contains its own provisions for the Secretary to inform "national,

State and local medical associations" etc, with information about investigational drugs. While the provision directs that information distributed under an expanded access program shall be "the same type of information" as that required by Section 113, Congress did not authorize the inclusion of expanded access information in the clinical trial data bank. FFDCA § 561(c); 21 U.S.C. § 360bbb(c).

3. Avoiding Duplication With Other Registries and Databases

NIH should address several questions associated with duplication with other databases and registries. Would it be practical to merge or otherwise provide computer-based links to the Physician Data Query (PDQ) database, AIDS Clinical Trial Information Service (ACTIS), and the NIH database? NIH should implement Section 113 in a manner that integrates these databases and registries, so that sponsors need not submit duplicate data to multiple sources and so that patients need not search multiple locations for the same type of information. If these different databases and registries are not harmonized, one could imagine that a sponsor studying Kaposi's Sarcoma could be asked to submit to three separate databases. This could become an unnecessary burden to study sponsors and would not provide patients with a single comprehensive source for information.

4. When Sponsors Must Submit Information

Under Section 113, sponsors must submit information to the data bank 21 days "after the approval of the protocol" for the clinical study. PHSA § 402(j)(3)(A); 42 U.S.C. § 282(j)(3)(A). Nothing in Section 113 specifies what constitutes the pertinent "approval," and the statutory reference is not self-evident. For example, FDA does not approve protocols. IRBs "approve" protocols, but this may occur weeks or even many

months before study initiation. Accordingly, NIH should provide a meaningful and constructive interpretation of this ambiguous provision; one workable approach would be to provide that information should be submitted to the data bank within 21 days of the first patient's enrollment in the protocol.

5. Ensuring the Integrity of Information in the Data Bank

In order to preserve the integrity of the information in the data bank, NIH should ensure that registry information is updated on a regular and ongoing basis. For example, changes should be made to the data base by NIH within five business days of the receipt of initial data or revisions from data sponsors. In addition, NIH should consider mechanisms for ensuring that information is accepted only from designated representatives of a sponsor.

6. Advertising for Study Subjects

Listing information in the data bank should not constitute advertising for patient recruitment, as previously defined by FDA in its Information Sheet "Advertising for Study Subjects" (February 1989), and should not therefore be subject to a specific requirement for IRB approval prior to public dissemination. Imposing such a requirement would hinder the public availability of such information and run counter to the purposes of Section 113. As such, FDA should confirm that information submitted to the data bank is exempt from the relevant 21 C.F.R. Part 50 and Part 56 requirements, and that IRB approval is not required before the information is submitted to the data bank.

7. Applicability to All Trial Sponsors

Section 113 expressly applies to all clinical trials of experimental treatments for serious or life-threatening diseases and conditions, whether federally or privately funded. PHSA § 402(j)(3); 42 U.S.C. § 282(j)(3). See also S. Rep. No. 105-43 at 67 (1997) (providing for the establishment of a registry of "both publicly and privately funded" clinical trials). In implementing Section 113, NIH should ensure that the requirement to submit information to the data bank applies to all trial sponsors, including corporate sponsors, sponsor-investigators, academic institutional sponsors, and governmental agency sponsors such as NIH itself and the Centers for Disease Control and Prevention.

8. Clinical Trial Results

As clearly provided in Section 113, no one is required to provide information on clinical trial results for the data bank. PHSA § 402(j)(3)(B); 42 U.S.C. § 282(j)(3)(B). As a general matter, including clinical trial results in the data bank raises a number of issues, including (1) the potential implication of NIH/FDA endorsement of the results; (2) the improper promotion of an investigational drug in contravention of 21 C.F.R. § 312.7; and (3) the public dissemination of preliminary results that may not agree with the final data once available.

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Section 113 of the FDA Modernization Act establishes a valuable mechanism for providing greater information to the public about clinical trials for serious and life-threatening diseases. The public health can benefit from giving patients increased access to the drug development process and to studies that may better define improved methods of treatment and medicines, as well as restore or maintain the patients' own wellness.

Care must be taken in implementing this new program, however, to ensure that the information disseminated to the public is of a rigorous nature, and that the program neither compromises the proprietary status of sponsor data nor creates administrative burdens that delay the drug development process.